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STUDY DESIGN FOR A CASE–CONTROL INVESTIGATION OF CELLULAR TELEPHONES AND OTHER RISK FACTORS FOR BRAIN TUMOURS IN ADULTS

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Abstract — The aetiology of brain tumours is poorly understood. Due, in part, to public concern about a postulated relationship between the use of cellular telephones or other increasingly prevalent environmental exposures and the incidence of brain cancer in adults, the National Cancer Institute is collaborating with three US hospitals in a comprehensive case–control study of malignant and benign brain tumours. Factors under consideration include use of cellular phones and other wireless communication devices, workplace exposures to chemical agents and electromagnetic fields, dietary factors, family history of tumours, genetic determinants of susceptibility, home appliance use, reproductive history and hormonal exposures, viruses, medical and dental exposure to ionising radiation, and other aspects of medical history. Approximately 800 newly diagnosed brain tumour cases and 800 controls were enrolled at hospitals in Boston, Phoenix and Pittsburgh from 1994 to 1998. Cases include all adults (age ≥ 18 y) newly diagnosed with a histologically confirmed intracranial glioma, histologically confirmed intracranial meningioma or acoustic neuroma. Controls are patients admitted to the same hospitals as the cases, and treated for any of a variety of non-malignant conditions. Key features of the study include its large size, the emphasis on rapid ascertainment of incident cases and interview of study subjects rather than surrogate respondents, the use of detailed, job-specific questions developed by industrial hygienists to ascertain occupational exposures, and the storage of blood samples for future evaluation of inherited susceptibility, biomarkers of exposure and gene–environment interactions.

INTRODUCTION

Brain cancer is among the most feared of cancers yet also is among the least well understood[(1)]. Incidence rates rose an average of 1.2% per year in the US during the 1970s and early 1980s, but have remained fairly stable since the mid-1980s, except among the elderly[(2)]. Although it seems likely that the pattern is mostly attributable to improved detection and reporting of brain tumours[(3–5)], some observers contend that the increase is real and evidence that exposure to one or more important environmental carcinogens has increased[(6–9)]. There has been widespread attention in the media to the possibility that the microwave frequency radiation emitted by hand-held cellular telephones causes brain cancer. Hand-held cellular phones were introduced to the market in 1984[(10)] and not in common use until the 1990s, so they cannot explain an increase in incidence of brain tumours before the mid-1980s. Other environmental agents that have attracted attention and concern in the context of this putative secular trend include industrial chemicals, pesticides, food additives (most recently, aspartame) and magnetic or electric fields[(6–9)].

In response to such concerns, and to explore a variety of other leads concerning possible causes of malignant and benign brain tumours, the US National Cancer Institute (NCI) is collaborating with three major medical institutions on a comprehensive aetiological study that is addressing a wide range of environmental, behavioural and genetic factors. The study design incorporated distinctive features that might be applicable in other studies of brain tumours or other chronic diseases, particularly with respect to occupational exposures. Herein, an overview of study methods and preliminary descriptive information concerning study participants is presented.

METHODS

Setting

The study is being conducted at hospitals in three large cities in the United States: St Joseph's Hospital and Medical Center (including Barrow Neurological Institute) in Phoenix, Arizona; Brigham and Women's Hospital in Boston, Massachusetts; and Western Pennsylvania Hospital in Pittsburgh, Pennsylvania. Criteria for choosing

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participating hospitals included that the hospital be in an urban setting and treat a large number of newly diagnosed adult brain tumour patients each year, that interested clinical collaborators with extensive experience in clinical research studies of brain tumours could be identified, and that other epidemiological studies of brain tumours not be in progress at that institution. Data collection began in 1994 and was completed in 1998.

Enrolment of cases and controls

Eligible cases were individuals newly diagnosed with an intracranial glioma, intracranial meningioma or acoustic neuroma and seen at one of the participating hospitals during the indicated time period. Histological confirmation was required, except for acoustic neuroma, for which a diagnosis based on a magnetic resonance imaging (MRI) scan was sufficient. Additional eligibility criteria included: age at enrolment $\geq$ 18 y, residence within 50 miles of the hospital (or within the state of Arizona for the Phoenix centre) and ability to understand English or Spanish. Some brain tumour patients enrolled in the study were diagnosed elsewhere and then referred to the participating hospital for treatment or other services. The operational definition of 'newly diagnosed' was that a patient be seen at the participating hospital within eight weeks of the date of first microscopic diagnosis. The majority of cases were interviewed within three weeks of microscopic diagnosis. Pending final determination of eligibility, enrolling approximately 500 patients with glioma, 200 with meningioma and 100 with acoustic neuroma is anticipated. Separate analyses will be conducted for each of these tumour groups. The occurrence of multicentric tumours and location of tumour(s) within the cranium, including laterality and lobe of brain, were documented based on radiological and surgical reports.

The control series consists of patients admitted to a wide array of services (including neurological, neurosurgical, general surgical, urological, cardiac, pulmonary, gastrointestinal and trauma) at the same hospitals as the cases for any of a variety of other, non-malignant conditions. For a patient to be eligible, the pre-hospitalisation duration of symptoms for the primary condition associated with the current admission could not exceed five years, but more than 90% of patients were interviewed within one year of onset of symptoms. Controls were frequency-matched to cases, in a 1:1 ratio, based on hospital, sex, race, age and proximity of residence to the hospital. Age, language, and geographic restrictions applied equally as for cases, and accrual of cases and controls occurred contemporaneously. The algorithm used to guide the frequency matching incorporated current data about subject accrual and updated the target numbers for controls with specified characteristics at each hospital on a weekly basis[11]. The choice was to include a wide variety of conditions in the control series, rather than just several, because many different exposures are to be evaluated. During data analysis, different subgroups of controls may be excluded from specific analyses, contingent on the *a priori* suitability of the illness or condition for evaluation of the particular risk factor under consideration.

Research nurses with extensive experience at their respective hospitals served as study coordinators. They were knowledgeable about hospital organisation and procedures, knew who the key contact persons were, and had strong support from collaborating neurologists, neurosurgeons, neuro-oncologists, radiation oncologists, other physicians, and nursing, laboratory and administrative staff. They monitored hardcopy records and computerised databases (admission, surgery, neurology, neurosurgery, radiology, pathology and other departments or services as necessary) on a daily basis and communicated with nurses and other hospital staff several times per week to ensure rapid ascertainment of potentially eligible cases and controls. They also attended weekly brain tumour conferences at which physicians presented data for new cases and discussed treatment plans. These redundant mechanisms helped to ensure complete and timely ascertainment.

Physicians who regularly treat patients in the services from which cases and controls were enrolled were provided with a description of the study. When potentially eligible patients were identified, attending physicians were contacted to request permission to approach individual patients. After obtaining physician approval, study coordinators sought the informed consent of patients, or a family member if the patient was incapacitated. Very few physicians denied access to their patients, and 92% of contacted eligible cases and 86% of contacted controls (or their proxies) agreed to participate in the interview phase of the study.

Power

At the inception of the study in 1993, there were an estimated 3 million-plus hand-held cellular telephones in use in the US. On the belief that the prevalence of cellular phone users is greater in urban than in rural areas, and among adults rather than children, it was assumed that a minimum of 2% of controls in the present study would have used hand-held cellular phones on a regular basis, defined as at least two calls per week. If so, a study of 800 cases and 800 controls would have 80% power to detect a relative risk (RR) of 2.1 ($\alpha = 0.05$, one-sided) and 99% power to detect a RR of 3.0. For glioma, comprising 500 of the 800 cases, the study would have 80% power to detect a RR of 2.3. For acoustic neuroma, the power to detect the same RR would be 48%.

The growth in use of cellular phones has been rapid, and our initial estimate of prevalence of exposure was probably too low, perhaps by a factor of several-fold. If so, the power could be greater than indicated above, but only if the latency period is very short. Widespread

use of cellular telephones is a recent development, and insufficient time has passed to accomodate a lengthy cancer induction period. However, it is widely assumed that, if magnetic fields cause cancer, they act at a late stage in the process. Furthermore, the study was initiated, in part, because of public concern that gliomas occurring *at the time* were caused by cellular phones. The present study should be able to clarify whether these concerns were well founded, but it will have limited power if the induction period is greater than five years.

The preceding calculations can be generalised to other exposures and indicate that the study should have adequate power for exposures with prevalences exceeding several per cent.

Interview and questionnaire

Information about risk factors was obtained in several stages. First, a structured personal interview was administered in the hospital by the research nurse shortly after the patient's diagnosis or admission. This interview covered use of portable telephones, occupational history, hobbies with potential for solvent exposures, personal and family medical history of selected diseases, reproductive history, and use of tobacco and hair colouring products. Information about religion, highest level of schooling completed, marital status, place of birth, household income and type of medical insurance coverage also was collected.

The interview involved intricate branching and skip patterns and was administered using a computer-assisted technique, which readily accomodated a complex interview structure and allowed for the incorporation of range and consistency checks while the interview was in progress. The computer-assisted personal interview (CAPI) program was installed on laptop computers, and the interview was administered at the patient's bedside or other suitable location in the hospital. Each interview was audiotaped, subject to the patient's consent, and audiotapes became part of each subject's file, with due safeguards to ensure confidentiality. Close family members, preferably spouses, were encouraged to assist the subject in recalling past events or habits. For each section of the interview, the interviewer recorded whether the subject, proxy, or both provided most of the answers. If the subject and proxy disagreed about the answer to a particular question, and the disagreement could not be resolved, the subject's response was recorded. A translator assisted with the interview for Spanish-speaking subjects who did not speak English. On average, the interview lasted approximately one and one half hours.

In addition to the personal interview, each subject or his or her proxy was given a supplemental, self-administered paper questionnaire covering diet, alcohol consumption, vitamin supplements and home use of electrical appliances. The study coordinator provided detailed instructions and a stamped return envelope. The patient was encouraged to complete the questionnaire with the assistance of a family member while in the hospital. The study coordinator offered to assist if the patient was unable to fill out the form by him- or herself. Patients who failed to return the questionnaire were contacted by telephone up to two times to remind them or offer assistance. Study participants were paid a small sum in compensation for their time. All completed self-administered questionnaires were keyed into the computer twice, and data records were compared to detect errors in data entry.

Patients were enrolled in the study even if seriously impaired, but the interview sometimes was delayed. Surrogate respondents were used for aphasic subjects or those who did not recover sufficiently to participate themselves. If a patient's physician advised that significant improvement was unlikely, a surrogate, preferably a spouse, was interviewed at the earliest possible time. The time period during which the surrogate had known the patient was recorded. As of June 1996, nine per cent of case interviews and four per cent of control interviews had been conducted with a surrogate only, that is, without the participation of the study subject. For each section of the interview, the interviewer assigned a subjective rating for the quality of information obtained from the study participant.

The interview and self-administered questionnaire were pre-tested on several brain tumour and other neurosurgical patients. Development of the questionnaire included cognitive pre-testing, in which the subject verbalises his or her thought process while answering each question[12]. Difficult, ambiguous, or misleading questions were then revised. A seven-day centralised training session was held for study coordinators from the three field centres. Multiple practice interviews were conducted during and after the training session. Each hospital was visited by supervisory staff shortly after the start of data collection, and again several months later, to ensure that proper procedures were being used. After six months of data collection, a three-day 'refresher' training session was held. Site visits continued on a semi-annual or annual basis. Frequent, regularly scheduled conference calls that included field and supervisory staff and NCI investigators provided a forum for discussing and resolving problems.

The audiotapes of interviews served several purposes. First, they provided the opportunity for ongoing monitoring of interviewer technique. Second, they served as a check on the accuracy of data entry. Supervisory staff listened to entire tapes while viewing keyed responses for 100% of the the first ten interviews for each interviewer (five cases and five controls), 10% of the next 100 interviews, and 5% thereafter. There was 100% review of the tapes for the portable telephone section of the interview. Third, data inconsistencies and outliers could be checked by listening to the tapes.

Blood samples and processing

For consenting cases and controls, 27 ml of blood (one 10 ml serum separator tube (SST) and two 8.5 ml acid citrate dextrose (ACD) tubes) were collected. Processing consisted of centrifuging the SST and ACD tubes, separating and aliquoting serum and buffy coat, and storage at −70°C at each hospital for up to one month prior to shipment on dry ice to an NCI biospecimen repository, where samples are stored at −70°C. The protocol was amended halfway though data collection to include obtaining viable lymphocytes. Collection of blood samples will enable us to explore a variety of questions pertaining to (i) inherited susceptibility, such as germ-line mutations in tumour suppressor genes and polymorphisms in metabolic or DNA repair enzymes, (ii) mutagen sensitivity and (iii) gene-environment interactions, and to assay biological markers of past exposure to environmental agents, including viruses. Blood samples typically were collected after surgery but before patients began radiotherapy or chemotherapy. Most cases will have been on steroidal medications before blood samples were obtained, and the possible effects of such treatment will need to be taken into account for some of the endpoints of interest.

SPECIFIC EXPOSURES UNDER STUDY

Cellular phones and other wireless communication devices

A variety of types of portable telephone exist, of which only one, hand-held cellular phones, has elicited concern as a possible cause of brain cancer[13]. Data were collected separately for hand-held, car (mobile), and transportable ('tote') cellular phones, as well as for cordless phones. Questions addressed type(s) of portable phones used, dates of first and last use and usual level of regular use. A recent study indicated a reasonably high correlation (Spearman $r = 0.79$) between self-reported weekly cellular phone use and the amount of use reported in billing records when the respondent reported being the sole user of the phone[14]. The questionnaire also asked about which hand usually was used to hold the phone when talking. This information can be used together with data on tumour location to assess the anatomic distribution of tumours with respect to radiofrequency energy deposition due to cellular phones[10]. However, the possibility of biased reporting of laterality of phone use by cases must be taken into consideration. It also is possible that impaired hearing due to a preclinical acoustic neuroma might influence hand choice.

Because of concern that some people might mistake cordless phones for hand-held cellular phones, and cordless phones are more commonly used, considerable care was given to making the distinction clear. A card displaying photographs of examples of different types of portable phones was shown, and the interviewer script included a description of distinguishing features, including that cellular phones typically had their own phone and billing numbers, whereas cordless phones could have the same numbers as other household phones. Names of local cellular service providers were mentioned, as these often were different from the regular (non-cellular) vendors.

Questions also were asked about use of ham and citizens' band (CB) radios, other portable two-way radios and walkie talkies and paging devices ('beepers'). Ham radios operate in the microwave frequency, and Milham[15] reported a non-significant excess of brain cancer among amateur radio operators. Pagers do not transmit signals at all. These devices were included not on the suspicion that they might cause brain tumours, but as a further basis for assessing the specificity of any observed associations between brain tumour risk and use of wireless communication devices.

Occupational exposures

Exposures of leading interest include organic solvents, vinyl chloride and other chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, fuels, engine exhausts, lubricating and other oils, pesticides, heavy metals, welding fumes, *N*-nitroso-compounds, magnetic and electric fields of different frequencies, and loud noise (for acoustic neuroma).

A comprehensive, lifetime occupational history was obtained, including start and stop dates for each job and job-specific questions developed by industrial hygienists to clarify the likelihood and extent of an individual's exposure to particular agents. These included questions about tasks performed, the frequency and duration of use of various types of equipment and chemicals, the presence of engineering controls and the use of personal protective gear. Detailed questionnaires were developed for 64 jobs, which were expected to cover at least 40% of the total jobs reported, based on experience from previous studies[16,17]. Modules of questions for specific jobs were invoked through computer linkages of responses to job-history questions with lists of synonyms used to describe jobs[18]. For other jobs, not covered by a module, generic questions were asked concerning job title, activities, and chemicals, materials, tools and equipment used. Full- and part-time jobs were distinguished.

A computer file containing all of the subject's responses to the occupational history section of each interview, but no identifiers of case–control status, was forwarded to an industrial hygienist at NCI within two weeks of completion of each interview. The industrial hygienist reviewed the data promptly to determine whether additional questions needed be asked to ascertain a person's likely extent of occupational exposure to specific agents. If additional information was required, the industrial hygienist provided, within 1–2 weeks, a

short list of follow-up questions to be asked in a subsequent ten minute interview. This follow-up interview was conducted in the hospital or by telephone if the patient had been discharged.

Exposure assessment will incorporate several features in an attempt to overcome limitations of previous studies. These limitations include involving an industrial hygienist only in the exposure assessment phase of the study, and not during study design and data collection; the assumption that all people holding a particular job have the same chemical (physical, biological) exposures and at the same levels; the semi-quantitative nature of exposure assessment, which hampers comparability across studies; and the lack of a systematic, formal structure to exposure evaluation, which lessens reproducibility. Our design builds upon the approach pioneered by Siemiatycki and colleagues[19–21] and methods described by Stewart and Stewart[16,17]. Details were discussed more fully by Stewart *et al*[18].

Family history

Data about family history of disease were collected systematically only for first-degree relatives. All living and deceased first-degree blood relatives were enumerated, including dates of birth and death. The respondent was then asked whether any of the first-degree relatives was ever told by a doctor that he or she had any of a series of types of neoplasm or selected other diseases. Age (or year) at diagnosis was recorded for each affected relative.

Diet and vitamin supplements

The dietary questionnaire included sections about frequency of consumption of fruits; vegetables; dairy products; grains; meat, poultry and fish; beverages (including alcohol) and artificial sweeteners. Data also were collected about types, frequency, and duration of use of vitamins and mineral supplements. Dietary exposures of special interest include nitrates and nitrites, fruits and vegetables, vitamins C and E, β-carotene and folate[1]. Nitrates and nitrites react with other dietary constituents in the stomach to form *N*-nitroso compounds (nitrosamides and nitrosamines). Nitrosamides are potent neurocarcinogens in a variety of mammalian species[22,23], and the possible role of *N*-nitroso compounds in the aetiology of brain tumours in humans has attracted considerable interest[24,25]. Fruits and vegetables, vitamins C and E, and folate have been identified as possibly being protective against brain tumours.[25,26].

Electrical appliances

The self-administered questionnaire also included sections concerning use of the following appliances: electric blanket, electric heating pad, electric water bed heater, bedroom humidifier, vibrating massage device, hair dryer, hair curling iron, electric shaver, sound system with headset, sound system without headset, television, computer, microwave oven and electric stove.

Reproductive history and use of exogenous hormones

The possibility of hormonal involvement in the pathogenesis of brain tumours is suggested by gender differences in the incidence of specific types of tumour[1,27], associations with reproductive factors in epidemiological studies[28,29] and results of animal experiments[30,31]. Steroid sex hormone receptors are expressed in human brain tissue[32–34] and may play a role in the natural history of some brain tumours. In the present study, women were asked about their menstrual and reproductive history, history of gynaecological surgery or radiotherapy, and use of birth control or oestrogen replacement medications.

Other

Other exposures addressed in the interview include cigarette smoking, use of chewing tobacco and snuff, use of hair dyes (distinguished as to colour and degree of permanency), and history of selected diseases, head trauma, and therapeutic or diagnostic irradiation of the head or neck area. Cranial radiotherapy is one of very few clearly established causes of brain tumours[1].

PROGRESS TO DATE

As of September 1998, more than 800 cases and 800 controls had been interviewed, but results for this sample are not yet available. A preliminary inspection of the data was carried out in June of 1996 for the 325 cases and 290 controls enrolled at that time. Selected characteristics of these persons are presented in Tables 1 and 2. Seventy-one per cent of the cases were gliomas, 17% were meningiomas, and 11% were acoustic neuromas (Table 1). Overall, cases were split equally between males and females, but there were relatively more gliomas among males and more meningiomas and acoustic neuromas among females. The average age of cases was 52 years, and they were overwhelmingly of white race.

The prevalence of selected risk factors in data collected through mid-1996 are shown for cases and controls combined (Table 2). Nearly one third of study participants reported having used a hand-held cellular phone, although the proportion of regular users was considerably lower. Preliminary results for cases and controls combined indicate that 10% of study participants used hand-held cellular phones at least twice per week for at least three months (5.8% used such phones for at least 30 min per week for at least three months). Nearly

75% had used cordless phones, and about 5% reported having used ham radios. Approximately 2.5% reported having received radiotherapy to the face, head or neck one or more years prior to the time of the interview. One per cent of subjects reported having been diagnosed previously with neurofibromatosis, and 5.5% reported at least one first-degree relative with a brain tumour. More than half had used electric blankets, and more than one third had used hair curling irons. The relative frequencies of patients reporting vitamin supplementation were 30% for vitamin C, 20% for vitamin E and 7% for β-carotene. Preliminary occupational data were presented by Stewart *et al*[18].

Table 1. Characteristics of 325 cases and 290 controls accrued up to June, 1996.

Characteristic	Cases (%)	Controls (%)
Type of brain tumour		
glioma	232 (71.4)	NA
meningioma	56 (17.2)	NA
acoustic neuroma	37 (11.4)	NA
Sex		
male	163 (50.2)	132 (45.5)
female	162 (49.9)	158 (54.5)
Age at enrolment (y)		
18–29	30 (9.2)	37 (12.8)
30–39	39 (12.0)	58 (20.0)
40–49	81 (24.9)	63 (21.7)
50–59	57 (17.6)	51 (17.6)
60–69	64 (19.7)	48 (16.5)
≥ 70	54 (16.6)	33 (11.4)
Race		
White*	308 (94.8)	280 (96.6)
Black	9 (2.8)	7 (2.4)
Asian/Pacific Islander	3 (0.9)	0 (0.0)
American Indian	3 (0.9)	3 (1.0)
Unknown	2 (0.6)	0 (0.0)
City		
Phoenix	153 (47.1)	120 (41.4)
Boston	107 (32.9)	88 (30.3)
Pittsburgh	65 (20.0)	82 (28.3)
Interview respondent		
patient only	225 (69.4)	270 (93.1)
patient + co-respondent	69 (21.3)	9 (3.1)
proxy only	31 (9.3)	11 (3.8)
Self-administered questionnaire		
completed	270 (83.1)	220 (75.9)
refusal	45 (13.8)	66 (22.8)
other	10 (3.1)	4 (1.4)
Blood sample		
obtained	249 (76.6)	200 (69.0)
refused	47 (14.5)	65 (22.4)
other	29 (8.9)	25 (8.6)

NA: Not applicable
*Includes Hispanics and Mexican Americans.

SUMMARY

Several features that were incorporated into the design of the present study were intended to improve upon previous aetiological studies of brain tumours. First, only newly-diagnosed cases were enrolled, and, with the exception of acoustic neuroma, diagnoses had to be histologically confirmed. These restrictions reduce the likelihood of confusing causes of brain tumours with factors that influence their clinical course, of misclassifying one type of brain tumour for another, and of misclassifying metastases from tumours of sites other than the brain, important sources of uncertainty for tumours ascertained solely from death certificates. Rapid case ascertainment provides an opportunity to interview patients about past behaviours and exposures before the disease compromises their ability to recall this information or respond to questions.

The approach that is being used to address occupational exposures should improve upon methods used

Table 2. Frequency distributions for selected variables included in the interview and self-administered questionnaire, for 616 study subjects (cases + controls).

Characteristic	Number (%)
Wireless communication devices (*ever use*)	
hand-held cellular telephone	199 (32.3)
mobile (car) cellular telephone	121 (19.6)
transportable (tote) cellular telephone	103 (16.7)
cordless telephone	460 (74.6)
ham radio	33 (5.3)
Medical history	
head trauma	124 (20.1)
neurofibromatosis	6 (1.0)
multiple sclerosis	5 (0.8)
Family history	
brain tumour	34 (5.5)
other tumour of nervous system	10 (1.6)
leukaemia or lymphoma	28 (4.5)
epilepsy	31 (5.0)
Electrical appliance use (≥ 3× in life)*	
electric blanket	259 (51.8)
electric water bed heater	123 (24.6)
electric shaver	187 (37.4)
hair dryer	364 (72.8)
hair curling iron	183 (36.6)
microwave oven	466 (93.2)
Other*	
cigarette smoking (≥ 100 cigarettes in lifetime)	347 (56.2)
ever use of hair dyes	272 (44.1)
Vitamin supplements (> once/week for ≥ 6 months)*	
vitamin C	151 (30.2)
vitamin E	99 (19.8)
β-carotene	35 (7.0)

*Based on self-administered questionnaires for 500 study subjects.

in previous studies of occupation and brain cancer, some of which were based solely on usual occupation as reported on death certificates or in cancer registry data. Not only are such occupational histories incomplete, but persons holding the same job title often were incorrectly assumed to have experienced similar exposures. Furthermore, population-based case–control studies typically include a high proportion of proxy or next-of-kin interviews, and surrogate respondents often do not know the details of the subjects' work. In the present study, lifetime occupational histories were collected directly from most study subjects, and job-specific questions formulated by industrial hygienists were included to capture important within job-title variation in exposures. The study design also allowed for prompt review of work histories by an industrial hygienist and the opportunity for follow-up questioning to fill in gaps or resolve inconsistencies in interview responses.

The collection of blood samples — lymphocytes and sera — will provide an opportunity to address the possible role of inter-person differences in susceptibility to brain tumours[35–36], and, in conjunction with the interview data, to evaluate possible gene-environment interactions. Serologic testing for evidence of viral exposures also is planned. Family history data collected through this study will serve as a starting point for more detailed studies of familial associations and brain cancer.

The present study was initiated, in part, because of concern about the risk of brain cancer associated with the use of hand-held cellular phones. In response to recommendations of an international panel of experts[37,38], the International Agency for Research on Cancer recently organised an international group of investigators who also plan to conduct case–control studies to evaluate the role of cellular telephones and other factors in the aetiology of adult brain, head and neck tumours. Whatever the collective results of these studies show on the question of cellular telephones, it is hoped and anticipated that their broad scope will lead to the identification of avoidable causes of brain tumours, or of factors that offer protection.

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REFERENCES

1. Inskip, P. D., Linet, M. S. and Heineman, E. F. *Etiology of Brain Tumors in Adults.* Epidemiol. Rev. **17**, 382–414 (1995).
2. Ries, L. A. G., Miller, B. A., Hankey, B. F., Kosary, C. L. and Edwards, B. K. (Eds). *SEER Cancer Statistics Review 1973–1995: Tables and Graphs.* NIH Pub. No. 98–2789 (Bethesda: National Cancer Institute) (1998).
3. Helseth, A. *The Incidence of Primary Central Nervous System Neoplasms Before and After Computerized Tomography Availability.* J. Neurosurg. **83**, 999–1003 (1995).
4. Radhakrishnan, K., Mokri, B., Parisi, J. F., O'Fallon, W. M., Sunku, J. and Kurland, L. T. *The Trends in Incidence of Primary Brain Tumors in the Population of Rochester, Minnesota.* Ann. Neurol. **7**, 67–73 (1995).
5. Smith, M. A., Freidlin, B., Gloeckler Ries, L. A. and Simon R. *Trends in Reported Incidence of Primary Malignant Brain Tumors in Children in the United States.* J. Natl Cancer Inst. **90**, 1269–1277 (1998).
6. Davis, D. L., Hoel, D., Fox, J. and Lopez, A. *International Trends in Cancer Mortality in France, West Germany, Italy, Japan, England and Wales, and the USA.* Lancet **336**, 474–481 (1990).
7. Davis, D. L., Ahlbom, A., Hoel, D. and Percy, C. *Is Brain Cancer Mortality Increasing in Industrialized Countries?*, Am. J. Ind. Med. **19**, 421–431 (1991).
8. Davis, D. L., Blair, A. and Hoel, D.G. *Agricultural Exposures and Cancer Trends in Developed Countries.* Environ. Health Perspect. **100**, 39–44 (1992).
9. Olney, J. W., Farber, N. B., Spitznagel, E. and Robins, L. N. *Increasing Brain Tumor Rates: is there a Link to Aspartame?* J. Neuropath. Exp. Neurol. **55**, 1115–1123 (1996).
10. Balzano, Q., Garay, O. and Manning, T.J. Jr *Electromagnetic Energy Exposure of Simulated Users of Portable Cellular Telephones.* IEEE Trans. Vehicular Technol. **44**, 390–403 (1995).
11. Wilcosky, T., Inskip, P. D., Karlsen, R., Whelan, J., Linet, M. and Hatch, E. *Case-control Matching for Prospectively Enrolled Participants* (Abstract). Am. J. Epidemiol. **143**, s28 (1996).

12. Subar, A. F. and 12 others. *Improving Food Frequency Questionnaires: a Qualitative Approach Using Cognitive Interviewing.* J. Am. Diet. Assoc. **95**, 781–788 (1995).
13. Rothman, K. J., Chou, C.-K., Morgan, R., Balzano, Q., Guy, A. W., Funch, D. P., Preston-Martin, S., Mandel, J., Steffens, R. and Carlo, G. *Assessment of Cellular Telephone and other Radio Frequency Exposure for Epidemiologic Research.* Epidemiology **7**, 291–298 (1996).
14. Funch, D. P., Rothman, K. J., Loughlin, J. E. and Dreyer, N. A. *Utility of Telephone Company Records for Epidemiologic Studies of Cellular Telephones.* Epidemiology **7**, 299–302 (1996).
15. Milham, S. Jr *Increased Mortality in Amateur Radio Operators due to Lymphatic and Hematopoietic Malignancies.* Am. J. Epidemiol. **127**, 50–54 (1988).
16. Stewart, W. F. and Stewart, P. A. *Occupational Case-control Studies: I. Collecting Information on Work Histories and Work-related Exposures.* Am. J. Ind. Med. **26**, 297–312 (1994).
17. Stewart, P. A. and Stewart W. F. *Occupational Case-control Studies: II. Recommendations for Exposure Assessment.* Am. J. Ind. Med. **26**, 313–326 (1994).
18. Stewart, P. A., Stewart, W. F., Heineman, E. F., Dosemeci, M., Linet, M. and Inskip, P. D. *A Novel Approach to Data Collection in an Occupational Case Control Study.* Int. J. Epidemiol. **25**, 744–752 (1996).
19. Siemiatycki, J., Wacholder, S., Richardson, L., Dewar, R. and Gérin, M. *Discovering Carcinogens in the Occupational Environment.* Scand. J. Work Environ. Health **13**, 486–492 (1985).
20. Gérin, M., Siemiatycki, J., Kemper, H. and Bégin, D. *Obtaining Occupational Exposure Histories in Epidemiologic Case-control Studies.* J. Occup. Med. **27**, 420–426 (1985).
21. Gérin, M. and Siemiatycki, J. *The Occupational Questionnaire in Retrospective Epidemiologic Studies: Recent Approaches in Community Based Studies.* Appl. Occup. Environ. Hyg. **6**, 508–515 (1991).
22. Kleihues, P., Lantos, P. L. and Magee, P. N. *Chemical Carcinogenesis in the Nervous System.* Int. Rev. Exp. Pathol. **15**, 153–232 (1976).
23. Bogovski, P. and Bogovski, S. *Animal Species in which N-nitroso Compounds Induce Cancer.* Int. J. Cancer **27**, 471–474 (1981).
24. Preston-Martin, S., Yu, M. C., Benton, B. and Henderson, B. E. *N-nitroso Compounds and Childhood Brain Tumors: a Case-control Study.* Cancer Res. **42**, 5240–5245 (1982).
25. Bunin, G. R., Kuijten, R. R., Buckley, J. D., Rorke, L. B. and Meadows, A. T. *Relationship between Maternal Diet and Subsequent Primitive Neuroectodermal Brain Tumors in Young Children.* N. Engl. J. Med. **329**, 536–541 (1993).
26. McCredie, M., Maisonneuve, P. and Boyle, P. *Perinatal and Early Postnatal Risk Factors for Malignant Brain Tumours in New South Wales Children.* Int. J. Cancer **56**, 11–15 (1994).
27. Preston-Martin, S. *Descriptive Epidemiology of Primary Tumors of the Brain, Cranial Nerves and Cranial Meninges in Los Angeles County.* Neuroepidemiology **8**, 283–295 (1989).
28. Cantor, K. P., Lynch, C. F. and Johnson, D. *Reproductive Factors and Risk of Brain, Colon, and other Malignancies in Iowa (United States).* Cancer Causes Control **4**, 505–511 (1993).
29. Schlehofer, B., Blettner, M. and Wahrendorf, J. *Association between Brain Tumors and Menopausal Status.* J. Natl Cancer Inst. **84**, 1346–1349 (1992).
30. Avtsyn, A. P. and Yablonovskaya, L. Y. *Effects of Disturbances in the Hormonal Status on Experimental Brain Tumors.* Acta Unio Int. Contra Cancrum **20**, 1519–1522 (1964).
31. Hopewell, J. W. *The Hormone-dependence of Experimentally-induced Gliomas in the Rat.* Neuropathol. Appl. Neurobiol. **1**, 141–148 (1975).
32. Martuza, R. L., MacLaughlin, D. T. and Ojemann, R. G. *Specific Estradiol Binding in Schwannomas, Meningiomas, and Neurofibromas.* Neurosurgery **9**, 665–671 (1981).
33. Brentani, M. M., Lopes, M. T. P., Martins, V. R. and Plese, J. P. P. *Steroid Receptors in Intracranial Tumors.* Clin. Neuropharmacol. **4**, 347–350 (1984).
34. McEwan, B. S. *Non-genomic and Genomic Effects of Steroids on Neural Activity.* Trends Pharmacol. Sci. **12**, 141–147 (1991).
35. Bondy, M. L., Kyritsis, A. P., Gu, J., de Andrade, M., Cunningham, J., Levin, V. A., Bruner, J. M. and Wei, Q. *Mutagen Sensitivity and Risk of Glioma: a Case-control Analysis.* Cancer Res. **56**, 1484–1486 (1996).
36. Wiencke, J. K., Wrensch, M., Miike, R., Zuo Z.-F. and Kelsey, K. T. *Population-based Study of S-transferase mu Gene Deletion in Adult Glioma Cases and Controls.* Carcinogenesis **18**, 1431–1433 (1997).
37. McKinlay, A. *Possible Health Effects Related to the Use of Radiotelephones.* Radiol. Prot. Bull. **187**, 9–16 (1997).
38. Repacholi, M. H. *Low-level Exposure to Radiofrequency Electromagnetic Fields: Health Effects and Research Needs.* Bioelectromagnetics **19**(1), 1–19 (1998).